Linezolid in multidrug-resistant tuberculosis

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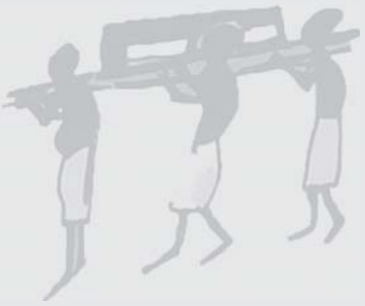

Chapter 5A

Comment on: Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients

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Sir,

We read with great interest the article "Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients" by Koh *et al.* in which they describe retrospectively examined records of one of the largest case series of patients treated with linezolid for multidrug-resistant and extensively drug-resistant tuberculosis (MDR/XDR-TB) (1). They describe long-term outcomes of 51 patients, whereas the previous study only described the short-term outcomes of 17 patients (2). Their objective was to evaluate efficacy, tolerability and adverse events of a 300 mg daily dose of linezolid in the treatment of MDR/XDR-TB. Based on a favorable treatment outcome of 78%, compared to 60 – 100% in literature albeit in smaller case series, they suggest that linezolid is effective against intractable MDR/XDR-TB at a daily dose of 300 mg. In our opinion it is difficult to draw this conclusion from the presented data. The lack of a control group makes it impossible to attribute favorable outcome in patients to a single drug such as linezolid as it is only a part of an expanded treatment regimen. Favorable treatment outcomes could very well be caused by other drugs of the expanded regimen the patients received.

To implicate efficacy of their linezolid containing regimen, Koh *et al.* make assumptions on the minimum inhibitory concentration (MIC) for linezolid for their population and the linearity of linezolid pharmacokinetics. They assume their patients are infected with *Mycobacterium tuberculosis* with a MIC of 0.25 mg/L for linezolid. Koh *et al.* base this on a recent study that described wild-type MIC distributions for linezolid and 6 other second-line drugs in 78 consecutive susceptible clinical isolates (3). Although most isolates had a MIC of 0.25 mg/L for linezolid, the wild-type MIC distribution ranged from 0.125 to 0.5 mg/L and an epidemiological cut-off value of 0.5 mg/L was suggested (3). The fact that we found the MIC to be 0.5 mg/L in eight isolates, 1 mg/L in eight isolates and even greater than 1 mg/L in one isolate in a previous study in 23 isolates (4), may raise some doubt about the assumption that all clinical isolates have a MIC value of 0.25 mg/L.

Koh *et al.* assume the pharmacokinetics of linezolid to be linear. Unfortunately, the pharmacokinetics of linezolid are not linear in TB patients as we have demonstrated in a previous study (5). Besides, substantial intra- and interpatient variability of linezolid in TB patients can be observed. We found the AUC_{0-12h} of 300 mg twice daily to be 56 mg*h/L but with an interquartile range (IQR) of 38.5 – 64.2 mg*h/L.

We agree with Koh *et al.* that for linezolid, the *in vitro* MIC to area under the free concentration time curve ($fAUC_{0-24h}$/MIC ratio) is often used as a predictive model for efficacy (5). Based

on the data of Schon *et al.* they suggest that a daily dose of 600 mg linezolid would lead to an fAUC of 56 mg*h/L, resulting in an fAUC/MIC ratio of approximately 100 for a wild-type MIC_{ECOFF} of 0.5 mg/L and of approximately 200 for the more common MIC of 0.25 mg/L. In both cases, the pharmacodynamic target of fAUC/MIC >100 is met. However, during the study period, DST as well as plasma concentration monitoring (therapeutic drug monitoring; TDM) were not performed for linezolid. This is very unfortunate since linezolid is the drug of interest in their study. As a consequence, it is unknown if the pharmacokinetic/pharmacodynamic target of $fAUC_{0-24h}$/MIC >100 is met. Therefore, in our opinion it is not correct to assume linezolid to be effective without DST and TDM for linezolid or without a control group.

Finally, we also do not support the conclusion that Koh *et al.* draw from the presented data being that a daily dose of 300 mg linezolid may be associated with fewer neuropathic side effects than a daily dose of 600 or 1200 mg linezolid. It was necessary to cease linezolid therapy in 14 patients (27%) due to neurotoxicity, which is within the range of the highly variable incidence of neurotoxicity of 4 – 89% at daily doses of 600 or 1200 mg as presented by Koh *et al.* in an overview of literature (1). Despite the daily dose of linezolid being low, the duration of administration of linezolid is long with a median of 278 days. This concurs with the current notion that the risk of adverse events of linezolid increases time-dependently (6).

Transparancy declarations

None to declare.

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